AMENDED CLAIMS

[received by the International Bureau on 24 May 1999 (24.05.99); original claims 1-5 and 8-9 amended; new claim 10 added. remaining claims unchanged (4 pages)]

1. The method of synthesizing combretastatin A-4 prodrugs as monosodium and disodium phosphate salts and trans-combretastatin A-4 prodrugs comprising:

admixing combretastatin A-4 with a phosphorylating agent to form a phosphate ester of combretastatin A-4 having protective groups thereupon;

selectively cleaving said phosphate ester protective groups with a cleaving agent to yield a phosphoric acid derivative of combretastatin A-4; and

treating said phosphoric acid derivative of combretastatin A-4 with sodium methoxide to yield combretastatin A-4 prodrug disodium phosphate, the combretastatin A-4 prodrug monosodium phosphate or a trans-isomer thereof as the ultimate product.

2. The method according to Claim 1 in which said phosphorylating agent is selected from the group consisting of dibenzyl phosphite/carbon tetrachloride, di-tert-butyloxy (N,N-diethylamido) phosphine and bis[2-(trimethylsilyl)ethoxy]N,N-diisopropylamidophosphine.

3. The method of Claim 1 in which said cleaving agent is selected from the group consisting of: iodotrimethylsilane, trifluoroacetic acid, and tetrabutylammonium fluoride.

4. The method of Claim 2 in which said cleaving agent is selected from the group consisting of: iodotrimethylsilane, trifluoroacetic acid, and tetrabutylammonium fluoride.

5. The method of claim 1 in which the ultimate product consists of X-combretastatin A-4 3'-O-phosphate wherein "X" is selected from the group consisting of cesium, calcium, lithium, magnesium, manganese, sodium, potassium and zinc.

6. The method of claim 1 in which the ultimate product consists of Y-combretastatin A-4 3'-O phosphate wherein "Y" is selected from the group consisting of imidazole, morpholine, piperazine, piperidine, pyrazole and pyridine.

7. The method of claim 1 in which the ultimate product is Z-combretastatin A-4 3'-O phosphate wherein "Z" is selected from the group consisting of adenosine, cinchonine, glucosamine, quinine, quinidine, tetracycline, and verapamil.

8. The method of synthesizing a trans-isomer of combretastatin A-4 Pro-drug comprising:

dissolving combretastatin A-4 in acetonitrile;

cooling the solution to -25°F;

adding carbon tetrachloride to the cooled solution with stirring;

adding 4-dimethylaminopyridine and dibenzyl phosphate to the cooled, stirred solution and warm to room temperature;

extracting the solvent from said room temperature solution to provide 3'-O-Bis(benzyl) phosphoryl- 3, 4, 4', 5 - tetramethoxy-(E)-stilbene;

admixing chlorotrimethyl silane with said 3'-O-Bis(benzyl) phosphoryl-3, 4, 4', 5 - tetramethoxy-(E) stilbene;

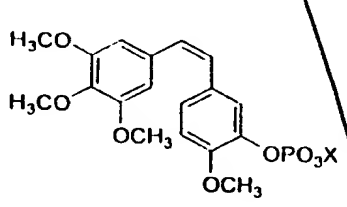
separating the solvent from the admixed solution with ethyl acetate to form an extract;

dissolving the extract in methanol;

adding sodium methoxide to said dissolved extract to form a second solution; and

removing the methanol from the second solution and recrystallizing the solid from said second solution to form a trans-isomer of combretastatin A-4 prodrug.

9. Combretastatin A-4 metal and ammonium phosphate prodrugs, and trans-combretastatin A-4 prodrugs having the structure



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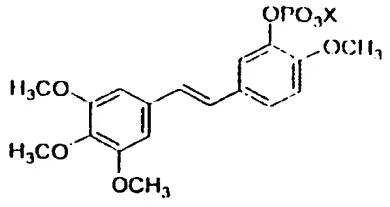

trans

wherein X is selected from the group consisting of cesium, calcium, lithium, magnesium, manganese, sodium, potassium, zinc, imidazole, morpholine, piperazine, piperidine, pyrazole, pyridine, adenosine, cinchonine, glucosamine, quinine, quinidine, tetracycline, and verapamil.

10. The method of claim 1 in which the ultimate product is recrystallized.